Prediction of Lipid Uptake by Prosthetic Heart Valve Poppets From Solubility Parameters

J. Moacanin and D. D. Lawson

Propulsion Division

H. P. Chin, E. C. Harrison, and D. H. Blankenhorn

University of Southern California

Most prosthetic heart valves currently implanted consist of a silicone rubber poppet situated within a metallic cage. Recent reports indicate that gradual deterioration of the poppet can occur and lead to serious valve malfunction. Physical changes (variance) observed in recovered prostheses include discoloration, swelling, and cracking. A major cause of variance is believed to be lipid accumulation. This article presents an assessment of the solubility of lipids in silicone rubber and other commonly used poppet materials. The analysis is based on solubility parameter theory that is based on principles derived from thermodynamic considerations. The results of this analysis predict that highly polar compounds, such as phospholipids or proteins, should not be present in silicone rubber poppets, which is in agreement with observations.

Introduction

Most prosthetic heart valves currently implanted consist of a silicone rubber poppet situated within a metallic cage. Recently, reports have indicated that gradual deterioration of the poppet can occur and lead to serious valve malfunction (References 1–6). Physical changes (variance) observed in prostheses recovered at autopsy or surgery include discoloration, swelling, and cracking; these may be accompanied by alterations in resiliency and specific gravity (References 1, 2, 4, 7, and 8).

A major cause of variance is believed to be lipid accumulation. Several laboratories have reported that all blood lipids are found in implanted valves, and occur in roughly the proportions usually found in human plasma (References 3, 6, 9, and 10). In our recent studies, however, no phospholipids or lipoproteins were found in any of the silicone poppets that were assayed, while the other lipids occurred in widely varying

proportions (Reference 11). These results strongly suggested that lipid infiltration is selective and that it may be influenced by the poppet material.

This article deals with an assessment of the solubility of lipids in silicone rubber and other commonly used poppet materials. The analysis is based on solubility parameter theory that is based on principles derived from thermodynamic considerations. The results of this analysis predict that highly polar compounds, such as phospholipids or proteins, should not be present in silicone rubber poppets, in agreement with observations.

Solubility Parameters for Poppet Materials and Lipids

In general, solubility, or miscibility, of two substances is to be expected if there is a decrease in the free energy of mixing, viz.,

$$\Delta F_{mix} = \Delta H_{mix} - T\Delta S_{mix}$$

Inasmuch as the entropy of mixing ΔS_{mix} is always positive (i.e., $-T\Delta S_{mix} < 0$), the enthalpy of mixing ΔH_{mix} will virtually determine solubility. The latter term for non-polar substances is positive and its magnitude is proportional to the difference of the respective solubility parameters δ (i.e., square root of the cohesive energy density):

$$\Delta H_{mix} \sim (\delta_1 - \delta_2)^2$$

Thus, the closer the solubility parameter values, the smaller the ΔH_{mix} will be and, consequently, the greater the decrease in ΔF_{mix} (References 12 and 13). For polar substances and those with strong tendency for hydrogen bonding, the definitions are somewhat tenuous. However, semi-empirical correlations are possible nevertheless. It follows from the above considerations that a lipid will dissolve in the poppet polymer material if the respective values are close to each other. Equal δ values, of course, will favor solubility most. However, mutual miscibility will exist for a range of values in the vicinity of the polymer solubility parameter δ_p. This range will depend in general on the particular polymer, but as a rule of thumb solubility will be likely for lipids whose solubility parameters δ_l are in the range $\delta_l = \delta_p \pm 2$. Inasmuch as the solubility parameter is a measure of intermolecular forces, it defines a number of molecular characteristics besides solubility. Consequently, there are a variety of methods to determine its value. Heats of vaporization data are commonly used for compounds which can be volatilized, whereas for polymers δ is usually determined indirectly from swelling measurements. For this work, literature data were used when available (Reference 14). However, for lipids such information could not be found. For these, estimates were made using semi-empirical correlations between the solubility parameter and refractive index (Reference 15).

Table 1 shows δ values for silicone rubber and other polymeric materials that are being used for valve poppets, whereas Table 2 shows values for a variety of lipids.

Table 1. Solubility parameters for poppet materials (References 14 and 16)

Material	Repeat unit	Density, g/cm³	(calories/cm³)$^{1/2}$
Poly(tetrafluoroethylene)	$-CF_2-CF_2-$	2.3–2.4	6.2
Poly(dimethylsiloxane)	$-Si(CH_3)_2-O-$	1.13	7.3–7.6
Poly(ethylene), high density	$-CH_2-CH_2-$	0.99	7.9–8.4
Poly(propylene)	$-CH(CH_3)-CH_2-$	0.90–0.94	8.2
Poly(ethylene terephthalate)	$-C_6H_4-COO-CH_2CH_2-OOC-$	1.46	9.7–10.7
Poly(methyltrifluoropropylsiloxane)	$-Si(CH_3)(C_2H_4CF_3)-O-$	1.4	8.5–11.0
Poly(formaldehyde), crystalline	$-CH_2-O-$	1.50	10.2–11.0

Discussion and Analysis

Most of the available information on the effect of blood on valve materials pertains to poly(dimethylsiloxane) elastomer, because most valves currently implanted have poppets made from this material. This elastomer contains about 20% silica filler. However, the powder, being crystalline and dispersed in the elastomer matrix, is very impermeable and is rather inaccessible to blood constituents. Thus, lipid uptake must be controlled by the properties of the elastomeric matrix, which has a solubility parameter δ of about 7.5.

Examination of Table 2 shows that δ values for lipids fall in two groups: for the weakly polar lipids, such as cholesteryl esters, triglycerides, and cholesterol, δ is about 9; whereas for the more polar phospholipids, δ is in excess of 16. Likewise, solubility parameters for proteins are again high, i.e., $\delta > 18$. It is apparent that δ for the first group is less than 2 units from that for the silicone elastomer and, consequently, well within the range necessary for miscibility. On the other hand, both phospholipids

Table 2. Solubility parameters of possible blood lipids estimated from refractive index data (Reference 15)

Lipids	$(\text{calories/cm}^3)^{1/2}$
Cholesterol and esters:	
Cholesteryl palmitate	8.4
Cholesteryl oleate	8.4
Cholesteryl stearate	8.4
Cholesterol	8.9
Triglycerides, α-glycerol ether esters and fatty acids (tripalmitin, tristearin, selachyl dioleate, oleic acid, stearic acid)	8.0 to 8.3
Lipid soluble vitamins	8.6 to 10.9
Hydrocarbon lipids (isoprene based and related alcohols)	8.2 to 8.5
Lipid bases (phosphorous and nitrogenous materials)	>16
Proteins	>18
Water	23

and proteins are far outside this range and therefore are insoluble. These considerations provide a straightforward explanation for our observations on recovered silicone rubber valve poppets (Reference 11), which showed the presence of the first group of lipids and absence of both phospholipids and proteins in poppets after implantation.

It has been reported that the extent of the vulcanization procedure affects lipid uptake (Reference 9). Vulcanization should not have a significant effect on δ, whereas it may greatly affect the crosslink density and the sol fraction, i.e., amount of soluble silicone. For given δ, the maximum (i.e., equilibrium) extent of swelling depends on these two factors (Reference 17). In general, a decrease in crosslink density and increase in sol content (both likely consequences of insufficient vulcanization) will increase the tendency to swell, or, in other words, favor lipid uptake. A similar effect may result from chemical degradation caused by excessive heating during vulcanization.

There is little information on variance in poppets made from other materials. We have examined recently two poly(formaldehyde) poppets which were implanted for rather short times. The results are preliminary but it was interesting to note that even though there appeared to be little foreign matter, some organic phosphorus was detected in one of the poppets. The δ value of near 11 for poly(formaldehyde) makes this result plausible, but it is still sufficiently far from 16, the value for phospholipids, to expect significant infiltration.

For the fluorosilicone elastomer we were able to arrive only at a range for δ. Calculations gave a low value, whereas solubility experiments (Reference 18) favor higher values. The higher value also seems to support the much lower lipid uptake for this elastomer as compared to silicone (Reference 9). Fluorosilicones would therefore appear to be promising. But their undesirably high density precludes their use in conventional configurations because for proper functioning the overall poppet density must approximate that of blood. Fluorocarbons have low δ, and their density is very high. Hydrocarbons such as poly(ethylene) and poly(propylene) do not have a favorable δ. However, their density is acceptable, and the highly crystalline forms of these polymers should be more impervious to lipids than silicone.

The presence of certain lipids and the absence of phospholipids and protein from silicone elastomer poppets is thus explained from considerations of solubility properties. However, the mechanism by which these lipids reach and infiltrate the poppet remains unknown. Lipids are present in plasma as spherical lipoprotein complexes that vary in size from a few hundred to perhaps 5000 Å and contain from about 1 to as much as 50% protein. The physico–chemical properties of lipoproteins appear to be dominated by the protein moiety, which suggests that their surface must be covered by protein. When the protein content is insufficient to form a monomolecular surface layer, it is believed that then the surface consists of a mixed protein-phospholipid layer, the latter being oriented with their charged groups at the surface (see, for example, References 19 and 20).

The silicone surface, like any foreign body in contact with blood, becomes covered with a protein layer. Inasmuch as lipid components exhibit considerable equilibration and exchange among the different lipoprotein classes (Reference 20), it is likely that they would behave similarly with respect to the protein layer on the silicone. Once on the surface, their solubility, which is higher in silicone than in plasma, will provide the necessary driving potential for permeation into the elastomer.

The importance of the blood flow to lipid uptake is suggested by the fact that most known cases of poppet variance are for the aortic valve; the blood flow velocity through this valve is the highest. The importance of the flow profile to the rate of collision with a surface has been analyzed in detail for the case of platelet deposition (Reference 21). Also, high shear forces would tend to deform lipoproteins and consequently increase the surface area, with the possible destruction of the continuity of the protein layer, thus favoring lipid deposition upon collision with the polymer surface. The fact that *in vitro* tests using lipid mixtures could not duplicate the extent of *in vivo* uptake (Reference 6) suggests that surface wetting by proteins and/or phospholipids is necessary for spreading of lipids at the surface. The importance of spreading at the surface could

be tested by studying *in vitro* the effect of various emulsifying and emulsion-breaking agents on lipid uptake.

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